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STUDIES AND INVESTIGATIONS. DAILY VARIATIONS OF URINARY EXCRETION OF 5-HYDROXY-INDOLE-ACETIC ACID IN NORMAL SUBJECTS

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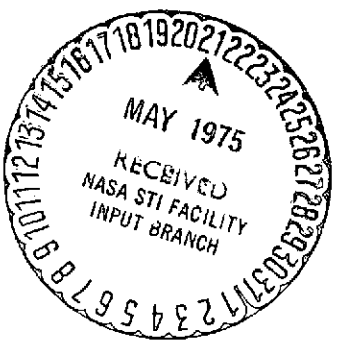

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16. Abstract Daily variations in the urinary excretion of 5-hydroxy-indol-acetic acid in 25 normal males. -- Urinary excretion of 5-hydroxy-indole-acetic acid, the main catabolite of 5-HT, was studied in 25 normal males at 8-hour intervals in the search for a circadian pattern. The method of Udenfriend was employed. A maximum nocturnal value and a minimum value between 8 a.m. and 4 p.m. were noted. The differences lacked significance, however.

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STUDIES AND INVESTIGATIONS. DAILY VARIATIONS OF URINARY EXCRETION OF 5-HYDROXY-INDOLE-ACETIC ACID IN NORMAL SUBJECTS

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The study of many endocrine activities as a function of time /57* has shown, in man and in experimental animals, that there are rhythmical variations with a predominantly circadian period.

Little work has been done on the urinary excretion of 5-hydroxy-indole-acetic acid, the main catabolyte of serotonin; the results available are rather vague and sometimes contradictory.

According to Johnsen and his co-workers (1958), the greatest elimination of this compound takes place between 9 a.m. and 3 p.m.; Peltlola and his co-workers (1960) found that about 50% is eliminated during the night; Schwemmle and his co-workers (1961) found no statistically significant differences between night and day. Bettendorf and his co-workers (1962) found, in women suffering from genital tumors, that the urinary excretion of 5-hydroxy-indole-acetic acid has its minimum value in the late afternoon and its highest value during the night, with an intermediate value in the morning.

The purpose of the present investigation was to find out whether there is a circadian course of the urine elimination of 5-hydroxy-indole-acetic acid in normal subjects. For this purpose urine was collected every 8 hours in a group of normal subjects, which were homogeneous with respect to age, sex and living habits.

MATERIALS AND METHODS

The work was carried out on 25 subjects, male college students, between the ages 20-25 and apparently healthy. They all belonged to the same college community, and followed a uniform daily schedule, (waking up at 7:30, breakfast at 8:30, lunch at 1:00, retiring at midnight). They no longer participated in strenuous physical activities nor were they subject to any kind of mental stress con- /58 nected with studying.

*Numbers in the margin indicate pagination in the foreign text.

They all received the same food, with foods high in serotonin content being excluded (bananas, mollusks, nuts, etc.).

All subjects were studied in the same period, i.e. during the winter.

The urine excreted from 8 a.m. to 4 a.m., from 4 p.m. to midnight, and from midnight to 8 a.m., was collected separately from each subject. Determination of 5-hydroxy-indole-acetic acid was carried out according to the colorimetric method of Udenfriend and co-workers (1955); this consisted of an extraction with chloroform and ether, and a reaction with naphthol-nitrous acid. The color obtained was measured spectrophotometrically at 540 mμ, against standard solutions of 5-hydroxy-indole-acetic acid.

RESULTS

The results obtained are given in Table I. They show that the greatest elimination of 5-hydroxy-indole-acetic acid takes place during the night (midnight to 8 a.m.), with an average value of 1.68 ± 0.77 mg, and the lowest elimination takes place between 4 p.m. and midnight with an average value of 1.27 ± 0.48. An intermediate value of 1.49 ± 0.71 mg is found between 8 a.m. and 4 p.m. A statistical evaluation using the student t test showed that these differences are not statistically significant.

DISCUSSION

The results obtained show that elimination of 5-hydroxy-indole-acetic acid in normal subjects has a circadian course characterized by a maximum during the night and by a minimum between 8 a.m. and 4 p.m.; the differences are not large, however, and there were considerable individual variations.

As a whole, these results do not disagree with those obtained by other authors; however, comparison is made difficult by the

TABLE I. URINARY EXCRETION OF 5-HYDROXY-INDOLE-ACETIC ACID AT VARIOUS TIMES OF DAY.

No.	Casw	Age	Time of Day 8am–4pm mg/8 h	4pm–12pm mg/8 h	12pm–8am mg/8 h
1)	B. L.	20	1.50	0.92	1,87
2)	C. S.	21	1.60	0,69	1,60
3)	N. L.	20	0.90	1,20	1,25
4)	N. M.	24	1,15	1,10	1.60
5)	G. O.	25	0,82	1,40	1.00
6)	T. M.	24	3,60	1,30	1.70
7)	R. P.	23	1,50	0,75	1,80
8)	R. L.	23	0,66	0,56	0,88
9)	U. U.	23	1,50	1,50	1,00
10)	Z. M.	24	0,92	1.00	0,93
11)	R. F.	25	2,15	0.64	1,65
12)	M. L.	21	1,64	1,50	1.10
13)	A. S.	20	1,40	1.40	1,60
14)	D. P.	22	1,20	0.86	0,90
15)	D. Pi.	23	1,10	0.80	1,20
16)	E. C.	25	2,50	2,30	1,60
17)	G. L.	24	2,70	1,90	2,10
18)	T. I.	23	2.10	1,30	2.10
19)	O. I.	23	1,30	1,90	1,60
20)	F. F.	21	2,00	1.40	2,30
21)	D. C.	23	1,00	2,30	3,00
22)	S. G.	24	0,93	1,30	2,00
23)	C. L.	20	1.70	2.00	4.50
24)	P. P.	20	1.50	1,10	1,40
25)	E. L.	23	0.82	0.66	1,32
	Average value		1,49 ± 0,77	1,27 ± 0.48	16,8 ± 0,71

fact that we used a different fractionation procedure of the urine collected, and also because our study involved only normal subjects.

The significance of the daily course observed in the elimination of 5-hydroxy-indole-acetic acid is not readily interpreted, since it cannot be directly and immediately related to serotonin metabolism.

5-hydroxy-indole-acetic acid is the final metabolite of serotonin, in the blood and in the brain; as far as cerebral serotonin is concerned, this catabolyte can be considered as providing a direct index, since it expresses the amount of serotonin transformed in the central nervous system into 5-hydroxy-indole-acetic acid at different times of the day. Matters are not as simple regarding blood

serotonin: as is well known, serotonin in blood is not in the free state (it is rapidly catabolyzed when free), (Blashko,1960 a, 1960 b; Robinson, 1972), but as soon as it is put into circulation by hetero-/59 chromaffine cells, it is mostly incorporated in the platelets, which form a sort of protective envelope. The fate of blood serotonin is thus connected with that of platelets, thus it is possible that it may be affected by their average life and by the circadian rhythm of the cellular activity in those areas where distribution or sequestering of platelets takes place, with liberation of the serotonin contained in them (Goldek, 1950; Halberg, 1967).

This field of study is still hazy, both experimentally and clinically.

It is not surprising, from what we have said above, that no well defined relationship has yet been found between circadian levels of blood serotonin (Genefke, 1968; Fogari et al., 1973), and the levels of urinary excretion of 5-hydroxy-indole-acetic acid; it should be kept in mind that a decreased urinary excretion of this compound does not necessarily have to correspond to a decrease in serotonin blood concentration; as a matter of fact it may occur as a consequence of a decreased liberation of serotonin from the platelets, and might thus be accompanied by an increase of its blood concentration; theoretically the two curves expressing the daily course of blood serotonin level and the urinary 5-hydroxy-indole-acetic acid level might have opposite courses.

In any case, the factors responsible for the circadian course that we have observed are difficult to interpret. This work confirms only the fact that in any research on the metabolism of biological amines circadian rhythms should always be taken into account.

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